April 2, 1947.

Dear Luria-

Your manuscript arrived this morning, and I have read it once quickly. Allow me to offer my congratulations on a well-written and very useful paper. I have some comments which are provoked by the paper, but are not intended as criticisms of it, except that in the bibliography, references 91 and 92 should be interchanged if the text is to remain unaltered. You may have overlooked this in correcting proof.

The phenomenon of phase variation deserves some genetic interpretation. In Salmonella, the alternate phases may be controlled by the intermutable allelomorphic states of a single gene, but in addition the composition of each phase can be altered separately, presumably by mutational loss. The phenomenon probably cannot be elucidates without recombinational analysis.

As to the mechanism of 'Dauermodifications' I think the recent work of Kimball on acquired resistance to antibody in Paramecium is the clearest answer, and may be generally applicable.However, one should not expect to find evidence for cytoplasmic systems in studies on mutational variations for this reason. Variation controlled by gene mutation will occur following a single discrete act: gene mutation. Cytoplasmic variation would demand the simultaneous occurrence of many 'mutations' if the entire set of plasmagenes is to be altered. It would appear more profitable to investigate natural groups which have been genetically isolated from one another for evolutionarily significant periods. The only exceptions are when differential growth rates of cells and plasmagenes can be established.

Finally, I would suggest that the credit for the first clearcut (albeit unsuccessful) genetic approach to bacterial gene recombination be given to Sherman and Wing, of whose work Gowen and Lincoln's is essentially designed.

Thank you for your very kind treatment of our work in this laboratory. In answer to your question as to the multiplication of the 'sporophyte' there is evidence suggesting that the sporophyte undergoes immediate reduction, and is certainly not capable of prolonged proliferation. This evidence is based on the fact that the zygote can be made to occur in agar (i.e. the mutants are grown separately, washed and mixed immediately before plating) so that all the prototroph recombinants originating from a given fusion will be localized, in the same colony. The homogeneity of such colonies with respect to the segregation of Lac and V has been studied; only a small %age of the colonies are not essentially homogeneous, and contain different segregation types; the possibilities of accidental contamination with this frequency are such that no definite conclusion can be drawn; a similar result would also be anticipated if there were four viable products of meiosis as in spermatogenesis. The question will have to be restudied under conditions such that contamination can be minimized. (Conceivably, also the prototroph is an exceedingly rare recombination type, so that only a small fraction of segregants will be of this type, and the chances for 2 'sporophytes' derived from the same zygote giving prototrophs small; this is not likely.)

Just noticed: I think your account of Boivin's work is slightly in error; according to his reprints and correspondence, transformation to C2-S is not accomplished; either C1-R or C2-R can be transformed to C1-S, however. His work is summarized in an additional reference: Acta Helvetica Chim, 29:1338 1946. The claim that an enzymatic change is transformed is subject to qualification, as he has written subsequently that the same change may occur spontaneously.

I hope that you will not take amiss these unsolicited comments; please regard them as 'peripatetic ruminations.'

You mentioned the development of a method for enumerating the 'lethal gene loci' in phage: permit me to guess what it is: to study the ratio of plaques to the number of irradiated phage particles absorbed per bacterium in the T2-T4 system. The frequency of 'recombination types' in mixed infected bacteria being known or 100%, each two-particle infection will yield a plaque unless there is a lethal mutation common to both of them. Or, alternatively to measure the dose of radiation that is necessary to block out all the loci of one phage type as determined by the failure to recover recombinants when infections mixed with another marked type are studied.

Thank you for the cartoon which you enclosed with the manuscript. It would be too simple to counter all criticism, however, with this type of defense; I have not heard too much of it at any rate, and mostly it is justified.

I'll send the manuscript back shortly, after I've had a chance to study it more carefully.

Yours sincerely,

Joshua Lederberg.